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(54) Title: CAROTENOIDS AS ANTI-HYPERTENSION AGENTS

(57) Abstract: A composition for lowering blood pressure comprising an effective amount of a carotenoid selected from among a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin or mixtures thereof. Further disclosed is a method for lowering blood pressure.

CAROTENOIDS AS ANTI-HYPERTENSION AGENTS

FIELD OF THE INVENTION

The present invention relates to the field of carotenoid containing compositions and uses thereof in reducing blood pressure.

BACKGROUND OF THE INVENTION

Carotenoids commonly occur in red, yellow, orange and green fruits and vegetables. Carotenoids, either of synthetic or natural sources, are known to be added to food and are taken as nutritional supplements. Lycopene, beta-carotene, phytofluene, phytoene, astaxanthin and cathaxanthin are among the carotenoids which have been found to demonstrate beneficial effects on human health, particularly on the vascular system.

US 5,705,526 (Fujiwara , et al.) relates to a method for treating hypercholesterolemia in a patient in need thereof, which comprises administering to said patient a hypercholesterolemia therapeutic agent containing lycopene as an effective ingredient therein, wherein said lycopene is administered to said patient in an amount within a range of from 1 to 25 mg per day per adult. PCT/IL98/00286 in the name of Lycored Natural Industries Ltd. describes the use of a synergistic mixture of lycopene and vitamin E for inhibiting the oxidation of LDL in human blood, and thus effectively inhibiting the progression of atherosclerosis.

Hypertension, which effects a large number of the population, increases the risk of cardiovascular disease. Thus, there is much interest in methods for reducing blood pressure.

There are at least three known categories of methods for decreasing blood pressure in mammals:

1) Long term therapy on blood lipid profile - Treating atherosclerosis in order to increase the cross-sectional area of the blood vessel. Said treatment is usually via lowering LDL concentration and modifying LDL/HDL ratio in the blood, and preventing/inhibiting the oxidation of LDL in the blood.

2) Treatment of physical properties of the blood (e.g. lowering viscosity and inhibiting/preventing platelet aggregation);

3) Treatment of physical/mechanical properties of blood vessels (e.g. flexibility of the arterial wall and vasodilator response).

Hereinafter said categories referred to as Category 1, Category 2 and Category 3, respectively.

The effect of category 1 treatment on patients is usually noticeable after longer periods of treatment (e.g. more than 2 weeks), whereas treatment under categories 2 and 3 take effect within shorter periods of time (e.g. 2 days to 3 weeks).

Hypercholesterolemia and atherosclerosis which may cause hypertension, are treated according to category 1.

Galley *et al, Clinical Science* (1997) 92, 361-365, disclose an oral antioxidant synergistic combination comprising beta-carotene, vitamin E, vitamin C and other antioxidants, as effective in lowering blood pressure.

Therapeutic methods within Categories 2 and 3 employ drugs such as aspirin and vasodilating drugs such as nifedipine (hereinafter referred to as "conventional

anti-hypertensive agents). There are undesirable side effects associated with the use of said drugs. There is therefore a need for a method for lowering blood pressure which is according to categories 2 and 3, which does have said side effects and is based on natural products.

Thus, it is an objective of the present invention to provide a method for lowering blood pressure by administering natural products, by a method which is not in category 1.

It is a further objective of the present invention to provide a composition for lowering blood pressure by a method which is not in category 1.

Other objectives of the present invention will become apparent as the description proceeds.

SUMMARY OF THE INVENTION

According to one aspect, the present invention provides the use of a carotenoid selected from among a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof, for lowering blood pressure in a mammal, wherein said lowering of blood pressure is not according to Category 1.

According to a further aspect, the present invention provides a composition for lowering blood pressure in a mammal not according to Category 1, comprising a blood pressure lowering effective amount of a carotenoid selected from among a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin or mixtures thereof.

According to yet a further aspect, the present invention relates to a method of lowering blood pressure in a mammal; said method not being a member of category 1, comprising administering to said mammal an effective amount of a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof.

According to another aspect, the present invention relates to the use of a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof, in the preparation of a medicament for lowering blood pressure in a human not according to Category 1.

According to another aspect, the present invention relates to a pharmaceutical composition useful in lowering blood pressure in a human not according to Category 1, comprising an effective amount of a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof.

According to another aspect, the present invention relates to a solid dosage form useful in lowering blood pressure in a human by a method not being a member of Category 1, comprising an effective amount of a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof.

In yet a further aspect of the present invention, a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof, is added to functional foods, dietary supplements or drinks in order to lower blood pressure not according to Category 1.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following description is illustrative of embodiments of the invention. The following description is not to be construed as limiting, it being understood that the skilled person may carry out many obvious variations to the invention.

It has unexpectedly been found that the administration of certain carotenoids effect a relatively quick response in the reduction of blood pressure (2 days to 2 weeks).

Throughout the specification the term carotenoids refers to carotenoids of natural, artificial and synthetic sources.

The following embodiments of the invention refer to the lowering of blood pressure not according to Category 1.

According to a particular embodiment of the method of the present invention, about 0.1 to 50 mg per day of a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof, are administered to a subject in need of lowering blood pressure. The administration is preferably oral administration, however, all forms of administration which achieve a blood pressure lowering effective concentration of carotenoid in the blood, e.g. about 0.3 to 0.8 μM of lycopene, is suitable for the purposes of this invention. Administration may be by a single daily dose or multiple doses.

According to yet a further embodiment of the method of the present invention about 1-50 mg per day of lycopene are administered to a subject in need thereof. According to a particular aspect of the invention 5 to 20 mg are administered daily to a subject.

According to yet a preferred embodiment of the method of the present invention about 1 to 25 mg of lycopene are administered orally 2 times daily.

In yet a further embodiment of the method of the present invention about 3 to 50 mg of a mixture of carotenoids comprising lycopene (3%-15%), phytoene (0.3%-1%), phytofluene (0.3%-1%) is administered in order to lower blood pressure in a subject in need thereof. The foregoing mixture may further comprise beta-carotene (0.1%-0.3%) and vitamin E (0.5%-3%).

The composition according to the present invention comprises about 0.1-50 mg of a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof. The composition may further comprise pharmaceutically acceptable adjuvant, excepients and additives. The composition may be in the form of tablets, capsules, hard shell capsules, gel-caps, soft gels or any further form suitable for the method of administration.

According to a preferred embodiment of the composition, said composition comprises 1 to 5 mg of lycopene.

In yet a further embodiment the composition of the present invention, the composition comprises about 3 to 50 mg of a mixture of carotenoids comprising lycopene (3%-15%), phytoene (0.3%-1%), phytofluene (0.3%-1%). The foregoing mixture may further comprise beta-carotene (0.1%-0.3%) and vitamin E (0.5%-3%).

In yet a further embodiment of the method of the present invention, the aforementioned dosages of carotenoids may be administered in conjunction with other conventional

anti-hypertension agents. Accordingly, a pharmaceutical composition containing a conventional anti-hypertension agent and a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof, is a further embodiment of the present invention.

According to yet a further embodiment of the present invention, a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof, may be added to food stuff, functional foods, dietary supplements and drinks in order to lower blood.

EXAMPLES

Example 1

Design and Methods: Thirty-five grade I HT subjects, aged 40-65, without concomitant diseases, who required no blood pressure and/or lipid lowering drug therapy, were recruited from primary care clinics. Study participants entered a two weeks run in period for establishment of HT (hypertension) diagnosis and base line evaluation, then 4 weeks placebo and finally 8 weeks treatment periods.

Results: Our results demonstrate significant reduction in both systolic BP (blood pressure) from 144 to 135, average of 9 mmHg reduction, and diastolic BP, from 91 to 84, average of 7 mmHg reduction.

Example 2

A double-blind, placebo-controlled crossover study of lycopene consumption in 16 healthy young individuals. Each subject was studied at baseline and then given 15mg lycopene or placebo for two weeks and re-evaluated. A one-month lycopene administration free washout period followed, another lycopene administration was

administered prior to a final evaluation. Each evaluation included measures among other parameters also heart rate and blood pressure. During lycopene administration subjects showed a significant reduction in diastolic blood pressure as compared to placebo administration ($p<0.05$). Table 1 summarizes the results of this study.

Table 1

Physiological parameter	Baseline	Placebo	Lycopene
Systolic Blood Pressure (mmHg)	112±3	111±2	114±2
Diastolic Blood Pressure (mmHg)	70±2	70±2	66±2

While embodiments of the invention have been described by way of illustration, it will be apparent that the invention may be carried out with many modifications, variations and adaptations, without departing from its spirit or exceeding the scope of the claims.

CLAIMS

1) A method for lowering blood pressure in a mammal, said method not being a member of Category 1, comprising administering to said mammal a blood pressure lowering effective amount of a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof.

2) A method according to claim 1 in which said mammal is human.

3) A method according to claim 1 wherein the carotenoid is lycopene.

4) A method according to claim 1 wherein about 0.1-50 mg of a carotenoid or mixture of carotenoids are administered.

5) A method according to claim 4 wherein about 5-20 mg of a carotenoid or mixture of carotenoids are administered daily.

6) A method according to claim 1 wherein about 1-25 mg of lycopene are administered daily.

7) A method according to claim 1 wherein a carotenoid or mixture of carotenoids is administered in conjunction with a conventional anti-hypertensive agent.

8) A method according to claim 7 wherein lycopene is administered in conjunction with a conventional anti-hypertensive agent.

9) A method according to claim 1 wherein a mixture of carotenoids is administered.

10) A method according to claim 9 wherein the mixture of carotenoids comprises lycopene, phytoene and phytofluene.

11) A method according to claim 10 wherein the carotenoid mixture comprises about 3%-15% lycopene, 0.3%-1% phytoene and 0.3%-1% phytofluene.

12) A method according to claim 11 wherein about 3 to 30 mg of mixture are administered daily.

13) Use of a carotenoid selected from among a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, in the preparation of a composition for lowering blood pressure in a mammal, wherein said lowering of blood pressure is not according to Category 1.

14) Use according to claim 13 in which said mammal is human.

15) Use according to claim 13 wherein the carotenoid is lycopene.

16) Use according to claim 13 wherein 0.1-50 mg of a carotenoid or mixture of carotenoids is applied.

17) Use according to claim 13 wherein about 1-25 mg of lycopene is applied.

18) Use according to claim 13 wherein a carotenoid or mixtures thereof are applied with a conventional anti-hypertensive agent.

19) Use according to claim 13 wherein lycopene is applied with a conventional anti-hypertensive agent.

20) A composition for lowering blood pressure in a human by a method not being a member of Category 1, comprising an effective amount of a carotenoid selected from among a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof.

21) A composition according to claim 20 comprising an effective amount of lycopene.

22) A composition according to claim 20 comprising about 0.1 to 50 mg of a carotenoid or a mixture of carotenoids and a pharmaceutically acceptable adjuvant, excepient or additive.

23) A composition according to claim 20 comprising a mixture of carotenoids.

24) A composition according to claim 23 wherein the mixture of carotenoids comprises lycopene, phytoene and phytofluene.

25) A composition according to claim 24 comprising about 3%-15% lycopene, 0.3%-1% phytoene and 0.3%-1% phytofluene.

26) A composition according to claim 25 comprising about 3 to 30 mg of carotenoid mixture.

27) A composition according to claim 20, wherein said composition is intended for oral administration.

28) A composition according to claim 20 in the form of tablets, capsules, hard shell capsules, gel caps or soft gels.

29) A composition according to claim 20 further comprising a conventional anti-hypertensive agent.

30) A solid dosage form comprising an effective amount of lycopene useful in lowering blood pressure in a human by a method not being a member of category 1.

31) Use of a composition as described in claim 20 as an additive to food stuff, functional foods, dietary supplements and drinks.

32) A pharmaceutical composition for lowering blood pressure in a mammal, not according to Category 1, comprising an effective amount of a carotenoid selected from a group consisting of lycopene, phytofluene, phytoene, astaxanthin and cathaxanthin, or mixtures thereof.

33) A pharmaceutical composition according to claim 32 wherein the carotenoid is lycopene.

34) A pharmaceutical composition according to claim 32 comprising about 0.1-50 mg of a carotenoid or mixture of carotenoids.

35) A pharmaceutical composition according to claim 32 further comprising a conventional anti-hypertensive agent.

36) A pharmaceutical composition according to claim 32 comprising a mixture of carotenoids.

37) A pharmaceutical composition according to claim 36 wherein the mixture of carotenoids comprises lycopene, phytoene and phytofluene.

38) A pharmaceutical composition according to claim 37 wherein the carotenoid mixture comprises about 3%-15% lycopene, 0.3%-1% phytoene and 0.3%-1% phytofluene.

39) A composition according to claim 36 comprising about 3 to 30 mg of mixture of carotenoids.

40) A method substantially as described and exemplified.

41) A use substantially as described and exemplified.

42) A composition substantially as described and exemplified.

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 046 880 A (GAINER JOHN L) 6 September 1977 (1977-09-06) column 1, line 41 -column 4, line 2; claims 1-6 ---	1,2,4,5
X	EP 0 770 385 A (SUNTORY LTD ;ITANO REFRIGERATED FOOD CO LTD (JP)) 2 May 1997 (1997-05-02) page 5, line 50-55; claims 1-18 ---	1,2,4,5, 13-15
X	PATENT ABSTRACTS OF JAPAN vol. 017, no. 489 (C-1106), 6 September 1993 (1993-09-06) & JP 05 124958 A (YUKIO DATE;OTHERS: 01), 21 May 1993 (1993-05-21) abstract --- -/--	1,2,4,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kling, I

Form PCT/ISA/210 (second sheet) (July 1992)

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 012, no. 213 (C-505), 17 June 1988 (1988-06-17) & JP 63 014678 A (LION CORP), 21 January 1988 (1988-01-21) abstract	1,2,4,5
Y	WO 98 57622 A (NIR ZOHAR ;ZELKHA MORRIS (IL); AVIRAM MICHAEL (IL); FUHRMAN BIANCA) 23 December 1998 (1998-12-23) cited in the application page 6, line 5 -page 9, last line; claims 1-25; examples 1-3; table 1	1-42
Y	EP 0 759 294 A (FUJIWARA MUTSUNORI) 26 February 1997 (1997-02-26) cited in the application page 2, line 21 -page 8, line 16; claims 1-6	1-42
A	KNEKT P ET AL: "Antioxidant vitamin intake and coronary mortality in a longitudinal population study" AMERICAN JOURNAL OF EPIDEMIOLOGY, SCHOOL OF HYGIENE & PUBLIC HEALTH OF THE JOHNS, US, vol. 139, no. 12, 15 June 1994 (1994-06-15), pages 1180-1189, XP002119579 ISSN: 0002-9262 abstract	1-42
A	KOHLMEIER L ET AL: "LYCOPENE AND MYOCARDIAL INFARCTION RISK IN THE EURAMIC STUDY" , AMERICAN JOURNAL OF EPIDEMIOLOGY, SCHOOL OF HYGIENE & PUBLIC HEALTH OF THE JOHNS, US, VOL. 146, NR. 8, PAGE(S) 618-626 XP000965738 ISSN: 0002-9262 abstract page 624, paragraph DISCUSSION	1-42

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/IL 02/00054

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 - 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 40-42
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 40-42

Present claims 40-42 relate to a method, a use and to a composition defined by reference to the description, namely "as described and examplified"

The claims cover all methods, uses and compositions having the characteristic or property claimed in the examples and in the description.
The present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.2(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), and claimed in claims 1 to 39.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Ional Application No
PCT/IL 02/00054

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